IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Attorney Docket No. 040388/0110

In re patent application of

Jean-Francois BACH *et al.*

Serial No. 08/986,568 Group Art Unit: 1644

Filed: December 5, 1997 Examiner: F. VanderVegt

For: METHOD FOR TREATING ESTABLISHED SPONTANEOUS AUTO-IMMUNE DISEASES IN MAMMALS

DECLARATION UNDER 37 C.F.R. § 1.132

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

I, Terry Strom, declare as follows:

(1) I was graduated from the University of Illinois School of Medicine, Chicago, IL in 1966 and then trained in Chicago and Boston, MA as a nephrologist and immunologist. I have been a faculty member of Harvard Medical School since 1973. I became Professor of Medicine, Harvard Medical School in 1988.Currently, I am an immunologist/nephrologist and Chief of the Division of Immunology. Beth Israel Deaconess Medical Center. I have over 25 years of experience with the clinical and experimental use, in the context of autoimmunity and transplantation, of anti-T cell monoclonal antibodies. In this regard, I possess particular expertise relating to anti-CD3 antibodies.

(2) I have reviewed the arguments presented in the appeal brief for the captioned case, which I understand is filed contemporaneously with this, my declaration. I also understand that Examiner VanderVegt alleges that Chatenoud *et al.*, *Proc. Nat'l Acad. Sci. USA* 91:123-127 (1994), suggested that immunotherapy. employing a $F(ab')_2$ fragment of an anti-CD3 antibody. would induce a durable state of antigen-specific unresponsiveness.

For the reasons elaborated below, I conclude that a person knowledgeable in immunology, circa 1997, would not have expected a durable, antigen-specific unresponsiveness to result from administering anti-CD3 antibody fragments. Rather, it would have been the expectation then that a durable, antigen-specific unresponsiveness, of the sort obtained upon administration of whole anti-CD3

antibody, as taught by Chatenoud *et al.* (1994), arose from a release of immunoregulatory cytokines which is not observed when anti-CD3 antibody fragments are administered.

Thus, the knowledgeable reader of Chatenoud *et al.* (1994) would have expected the remission induced by treatment with CD3 antibody to be the result of cytokine-mediation of immune function. It was well-known at the time that the CD3 antibody used by Chatenoud *et al.* is a potent mitogen and, as such, triggers the release *in vivo* of a variety of cytokines. It also was well-known that two of these cytokines, IL-4 and IL-10, prevent the onset of diabetes in NOD mice. See Rapoport *et al.*, *J. Exp. Med.* 178: 87-99 (1993), and Pennline *et al.*, *Clin. Immunol. and Immunopath.* 71: 169-175 (1994). Therefore, it was expected that the durable, antigen-specific unresponsiveness, obtained upon administration of anti-CD3 antibody, arose from the mitogenic potential of the anti-CD3 antibody.

Since it was also well-known that $F(ab')_2$ fragments are non-mitogenic, a knowledgeable immunologist would have expected that immunotherapy, employing a $F(ab')_2$ fragment of an anti-CD3 antibody, would not trigger cytokine release and, therefore, would not induce a durable, remission of overt autoimmunity. Accordingly, I conclude that Chatenoud *et al.* (1994) would not have suggested that immunotherapy with such a $F(ab')_2$ fragment would induce a durable state of antigen-specific unresponsiveness.

(3) I declare further that all statements made herein of my knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements and the like are made with knowledge that willful false statement and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of this application or any patent issuing thereon.

Nov. 15, 1999
Date

Terry B. Strong
Terry Strong